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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,189	12/02/2003	Berkley Lynch	053529-5007-01	4272

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,189	LYNCH ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-172* is/are pending in the application.

4a) Of the above claim(s) *1-92,103-125,138 and 157-172* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93-102,126-137 and 139-156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/ Election/Restrictions

Applicant's election with traverse of Group VII and N-alkylated 2-oxo-pyrrolidine derivatives in the reply filed on January 30, 2006 is acknowledged. The traversal is on the ground(s) that Examiner has not established that Group IV and XI-XIV are patentably distinct from Group VII. Group IV, VII and XI-XIV should be group together because they comprise many same steps and starting materials. In addition, Applicant argues that the examination/search of Groups IV, VII and XI-XIV would not be a serious search burden on the examiner. This is not found persuasive because the steps, materials, equipments and end results are different in the Groups IV, VII and XI-XIV. For example, the method of discovering or modeling the interaction between a SV2 protein and the binding compound using the biochemical, physical or computer techniques does not necessarily achieve the same goal as to identify a compound useful for treating a neurological disease. In addition, the materials for screening a compound that is useful for treating a disease may be involved in using a disease animal model to evaluate whether the test compound has any efficacy, which is not required by the methods of modeling the interaction between the protein and the test compound. Since the steps and materials involved in the Group VII are different from those in Group IV, XI-XIV, the expected results are different. Therefore, Group IV, VII and XI-XIV are patentably distinct. In addition, the materials, steps and outcomes are different among these different Groups, indicating that the search is not co-extensive. A reference to one element would not constitute a reference to another. Therefore, the

examination/search of Groups IV, VII and XI-XIV would be a search burden on the examiner and the USPTO's resources.

The requirement is still deemed proper and is therefore made FINAL.

The error of classification on Group XIV is acknowledged. The classification for Group XIV should be classified in for example class 435, subclass 7.21.

Claims 1-172 are pending. Claims 1-92, 103-125, 138, and 156-172 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups I-VI and VIII-XI-XVII, there being no allowable generic or linking claim. Claims 93-102, 126-137, 139-156 are under examination in this office action.

Claim Objections

Claims 95 and 155 are objected to as encompassing non-elected subject matter.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the serial number of the Application is not listed in the first page of the combined declaration.

Drawings

The drawings are objected to because there is no legend indicating what open/filled circles represent in the figure 10. There is no label indicating what each lane represents in the blot shown in the figure 12. There is no legend indicating what open/filled histograms and the symbols represent in the figure 17. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93-102,126-137, and 139-156 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying the binding of levetiracetam (LEV) L059, LEV analog ucb30889, ucb-101282-1 binding to the levetiracetam binding site of SV2A protein, does not reasonably provide enablement for all LEV analogs/derivatives binding to the levetiracetam binding site of SV2A protein, or all compounds that modulate all different activities of all SV2 proteins and are useful for treating all neurological disorders associated with synaptic function, endocrinopathy or hormonal disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 93-102,126-137, and 139-156 are drawn to a method of identifying a compound/agent useful for treating a neurological disorder associated with synaptic function, endocrinopathy or hormonal disease comprising screening the test compound/agent with the activity of competing with the levetiracetam-binding site of SV2A protein. Applicant discloses that radioisotope-labeled levetiracetam (LEV) or ucb30889 is able to bind to brain membrane, and LEV is an anti-epilepsy drugs, which is through the regulation of inhibitory and excitatory synaptic transmission and Ca channel activity. However, Applicant fails to teach the conserved structure of analogs/derivatives of levetiracetam that are required for competing the binding of the levetiracetam-binding site of SV2A protein. There are at least three isoforms for SV2 proteins as stated in the specification. The instant specification fails to provide sufficient disclosures of whether all levetiracetam derivatives/analogs are able to bind to all SV2 proteins. In addition, the specification fails to disclose what other activities/functions of SV2 protein are. The specification does not provide sufficient guidance as to how to evaluate what other activities for SV2 and whether levetiracetam/its derivatives or the agents with the ability of competing with the levetiracetam-binding site of SV2 can regulate all the activities of SV2. In addition, although levetiracetam is a drug approved to treat epilepsy, Applicant has not provided any guidance of whether levetiracetam/its

derivatives or the agents with the ability of competing with the levetiracetam-binding site of SV2 can be useful for treating all neurological diseases associated with synaptic function, endocrinopathy or hormonal disease or the diseases recited in the claim 155. Applicant has not taught or provided any working species that these levetiracetam/its derivatives or the agents with the ability of competing with levetiracetam-binding site of SV2 are useful for treating all neurological disorders, endocrinopathy or hormonal disease except epilepsy.

In addition, there is insufficient guidance and direction as to make/use all analogs or derivatives of levetiracetam that bind to all SV2 protein. Applicant has not enabled one skilled in the art to make and/or use all analogs or derivatives of levetiracetam to bind to all SV2 protein and regulate all activities of SV2. Applicant has not taught the genus of the conserved structure of analogs/derivatives of levetiracetam to regulate all activities of SV2. In addition, Applicant has provided no guidance as to how these agents are useful for treating all neurological disorders associated with synaptic function, endocrinopathy or hormonal disease. Applicant has not provided enough guidance as to how to apply the findings of the binding levetiracetam to SV2A in treating all neurological diseases since levetiracetam has only been shown to treat epilepsy. In addition, Applicant has not disclosed any working species of anti-SV2A protein with the ability to compete the levetiracetam-binding site of SV2A protein that can regulate all SV2 activities. Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed method of identifying a compound/agent useful for treating neurological diseases comprising screening the test compound with the activity

of competing with the levetiracetam-binding site of SV2. Without such guidance, what activities of SV2 to be evaluated and whether the test agents can regulate all activities of SV2 are unpredictable indicating that undue experimentation is required to those skilled in the art while using the invention.

Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to the method of identifying a compound/agent with the activity of competing the levetiracetam-binding site of SV2A protein and being useful for treating neurological diseases associated with synaptic function.

Claims 93-102,126-137, and 139-156 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Applicant is in possession of levetiracetam or the compound listed in the claim 95. However, Applicant is not in

possession of all analogs, derivatives of levetiracetam or antibodies that binds to the levetiracetam-binding site of SV2A protein. Applicant has only disclosed a limited number of species; therefore, the skilled artisan cannot envision all contemplated possibilities of levetiracetam derivatives or all antibodies binding to the levetiracetam-binding site of SV2A protein recited in the instant claims.

The specification fails to define the particular conserved structure for analogs or derivatives of levetiracetam that are required for competing the levetiracetam-binding site of SV2A protein. The lack of sufficient limitations would therefore allow for any chemical structure/molecules to be a part of compounds, which may change the binding ability to the levetiracetam-binding site of SV2A. Therefore, the skilled artisan cannot envision all contemplated possibilities recited in the instant claims. Furthermore, Applicant fails to specify/describe the genus of "amines", the genus of "excitatory neurotransmitters" and the genus of "other amino acids, sugars, and organic ions" as recited in the claim 136. Similarly, Applicant fails to specify/describe the genus of "fragments" of the protein as recited in the claim 156. Applicant provides no working species for the genus of amines, the genus of excitatory neurotransmitters, the genus of other amino acids, sugars, organic ions, or the genus of fragments. One of skill in the art can not envision what particular structures/characteristics are required within these different genera. Since the structure/characteristics of these genera are not predictable, a skilled artisan can not contemplate the functional correlations of these different genera with the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention. A description of a genus of polypeptides/

compounds may be achieved by means of a recitation of a representative number of polypeptide sequences/chemical groups, defined by amino acid sequence/chemical structure, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Therefore, the method of identifying a compound useful for treating a neurological disorder comprising screening a derivative of levetiracetam or an agent competing with the levetiracetam binding site of SV2 have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 93-102 and 139-156 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what result is obtained/what activity of the SV2 protein is evaluated.

Claims 93, 130-132, 135, 137, and 139 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant fails to define the word "modulate" recited in the claims. A compound can either enhance or inhibit synaptic function and subsequently alleviate or treat a neurological disorder associated with synaptic function. Since Applicant has not limited the neurological disorder, whether an agent can enhance or inhibit the activity of SV2 is unpredictable, thus renders the claims indefinite. In addition, Applicant has not defined a particular activity of SV2 in the claim 93, which renders the claim indefinite.

Claims 94-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to analogs and derivatives of a compound or agent. The disclosure fails to set for the metes and bounds of what is

encompassed within the definition of such analogs and derivatives and thus the claims are indefinite.

Claim 135 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has not defined what is encompassed within the claimed substrate, therefore, the metes and bounds of the claimed invention cannot be determined.

Claims 94-102, 126-137 and 140-155 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The article "A" connotes that there is more than a single method encompassed within the base claim and since only a single method was set forth therein, it is unclear what, if any, additional methods are encompassed.

Claims 152 and 153 are rejected under 35 U.S.C. 112, second paragraph as lacking clear antecedent bases for "the agent". An amendment of the claim to recite "compound or agent" would overcome the rejection.

Obviousness-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 93-102, 139-154 and 156 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9-12,17-19, 22-25, 29,35, 37-40, 45-52, 54-57, 61-68, 71-74, and 78 of copending Application No. US/10/308,163 ('163). Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of identifying a compound with the activity of competing with the binding of levetiracetam to the levetiracetam binding site of SV2A or identifying compound of levetiracetam derivatives/analogs in this instant case encompass the view of the binding partner that modulates the binding of levetiracetam/its derivatives to SV2A in the method of identifying a binding partner for SV2A as stated in the claims of the Application No. '163. While language is not identical, the claims of the instant application and the copending application encompass the same scope of invention, which is to identify a compound

that can compete with the levetiracetam-binding site of SV2, wherein the test compound can be antibodies, analogs/derivatives of levetiracetam or any molecules that can compete with or modulate the binding of levetiracetam to SV2A. Thus the instant and copending Application claim the same and non-distinct inventions of the method for identifying a compound that can compete the levetiracetam binding site of SV2 with levetiracetam and useful for treating a neurological disorder associated with synaptic function.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 93, 97, 99, and 102 are rejected under 35 U.S.C. 102(a) as being anticipated by WO2003016475A2 published Feb 27, 2003, effective filing date Aug 14, 2001.

WO2003016475 teaches several molecules involved in pain conditions including SEQ ID NO:2793, SV2 protein, which has 100% identity to the instant SEQ ID NO:2. WO2003016475 also teaches a method for identifying a compound that regulates the activity of SV2A in the cells comprising contacting the cells with a candidate compound and measuring the activity of the test polypeptide in the cells. WO2003016475 further teaches a method for identifying a compound useful in treating pain and a pharmaceutical composition comprising one or more polypeptides or their antibodies recited in their disclosure. In addition, the candidate compounds include small molecule, protein, RNAi, antisense and antibody (see p. 12, third paragraph to p. 17, first paragraph).

The sequence search results disclose as follows:

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ADE56938
ID   ADE56938 standard; protein; 742 AA.
AC   ADE56938;
DT   29-JAN-2004  (first entry)
DE   Human Protein NP_055664, SEQ ID NO 2793.
KW   Human; pain; neuronal tissue; gene therapy;
KW   spinal segmental nerve injury; chronic constriction injury; CCI;
KW   spared nerve injury; SNI; Chung.
OS   Homo sapiens.
PN   WO2003016475-A2.
PD   27-FEB-2003.
PF   14-AUG-2002; 2002WO-US025765.
PR   14-AUG-2001; 2001US-0312147P.
PR   01-NOV-2001; 2001US-0346382P.
PR   26-NOV-2001; 2001US-0333347P.
PA   (GEHO ) GEN HOSPITAL CORP.
PA   (FARB ) BAYER AG.
PI   Woolf C,  D'urso D,  Befort K,  Costigan M;
DR   WPI; 2003-268312/26.
DR   GENBANK; NP_055664.
PT   New composition comprising two or more isolated polypeptides, useful for
PT   preparing a medicament for treating pain in an animal.
PS   Claim 1; Page; 1017pp; English.
CC   The invention discloses a composition comprising two or more isolated rat
     or human polynucleotides or a polynucleotide which represents a fragment,
     derivative or allelic variation of the nucleic acid sequence. Also
     claimed are a vector comprising the novel polynucleotide, a host cell
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comprising the vector, a method for identifying a nucleotide sequence which is differentially regulated in an animal subjected to pain and a kit to perform the method, an array, a method for identifying an agent that increases or decreases the expression of the polynucleotide sequence that is differentially expressed in neuronal tissue of a first animal subjected to pain, a method for identifying a compound which regulates the expression of a polynucleotide sequence which is differentially expressed in an animal subjected to pain, a method for identifying a compound that regulates the activity of one or more of the polynucleotides, a method for producing a pharmaceutical composition, a method for identifying a compound or small molecule that regulates the activity in an animal of one or more of the polypeptides given in the specification, a method for identifying a compound useful in treating pain and a pharmaceutical composition comprising the one or more polypeptides or their antibodies. The polynucleotide or the compound that modulates its activity is useful for preparing a medicament for treating pain (e.g. spinal segmental nerve injury (Chung), chronic constriction injury (CCI) and spared nerve injury (SNI)) in an animal (e.g. gene therapy). The sequence presented is a human protein (shown in Table 2 of the specification) which is differentially expressed during pain. Note: The sequence data for this patent did not form part of the printed specification, but was obtained in electronic form directly from WIPO at ftp.wipo.int/pub/published_pct_sequences.

SQ Sequence 742 AA;

Query Match 100.0%; Score 3911; DB 7; Length 742;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 742; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy       1 MEEGFRDRAAFIRGAKDIAKEVKKHAAKKVVKGLDRVQDEYSRRSYSRFEEEDDDDDFPA 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MEEGFRDRAAFIRGAKDIAKEVKKHAAKKVVKGLDRVQDEYSRRSYSRFEEEDDDDDFPA 60

Qy      61 PSDGYYRGEGTQDEEEGGASSDATEGHDEDDEIYEGEYQGIPRAESGGKGERMADGAPLA 120
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 PSDGYYRGEGTQDEEEGGASSDATEGHDEDDEIYEGEYQGIPRAESGGKGERMADGAPLA 120

Qy     121 GVRGGLSDGEGPPGGRGEAQRRKEREELAQQYEAILRECGHGRFQWTLYFVLGLALMADG 180
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 GVRGGLSDGEGPPGGRGEAQRRKEREELAQQYEAILRECGHGRFQWTLYFVLGLALMADG 180

Qy     181 VEVFVVGFVLPSAEKDMCLSDSNKGMLGLIVYLGMMVGAFLWGGLADRLGRRQCLLISLS 240
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 VEVFVVGFVLPSAEKDMCLSDSNKGMLGLIVYLGMMVGAFLWGGLADRLGRRQCLLISLS 240

Qy     241 VNSVFAFFSSFVQGYGTFLFCRLLSGVGIGGSIPIVFSYFSEFLAQEKRGEHLSWLCMFW 300
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     241 VNSVFAFFSSFVQGYGTFLFCRLLSGVGIGGSIPIVFSYFSEFLAQEKRGEHLSWLCMFW 300

Qy     301 MIGGVYAAAMAWAIIPHYGWSFQMGSAYQFHSWRVFVLVCAFPSVFAIGALTTQPESPRF 360
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     301 MIGGVYAAAMAWAIIPHYGWSFQMGSAYQFHSWRVFVLVCAFPSVFAIGALTTQPESPRF 360

Qy     361 FLENGKHDEAWMVLKQVHDTNMRAKGHPERVFSVTHIKTIHQEDELIEIQSDTGTWYQRW 420
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db    361 FLENGKHDEAWMVLKQVHDTNMRAKGHPERVFSVTHIKTIHQEDELIEIQSDTGTWYQRW 420

Qy    421 GVRALSLGGQVWGNFLSCFGPEYRRITLMMMGVWFTMSFSYYGLTVWFPDMIRHLQAVDY 480
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    421 GVRALSLGGQVWGNFLSCFGPEYRRITLMMMGVWFTMSFSYYGLTVWFPDMIRHLQAVDY 480

Qy    481 ASRTKVFPGERVEHVTFNFTLENQIHRGGQYFNDKFIGLRLKSVSFEDSLFEECYFEDVT 540
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    481 ASRTKVFPGERVEHVTFNFTLENQIHRGGQYFNDKFIGLRLKSVSFEDSLFEECYFEDVT 540

Qy    541 SSNTFFRNCTFINTVFYNTDLFEYKFVNSRLINSTFLHNKEGCPLDVTGTGEGAYMVYFV 600
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    541 SSNTFFRNCTFINTVFYNTDLFEYKFVNSRLINSTFLHNKEGCPLDVTGTGEGAYMVYFV 600

Qy    601 SFLGTLAVLPGNIVSALLMDKIGRLRMLAGSSVMSCVSCFFLSFGNSESAMIALLCLFGG 660
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    601 SFLGTLAVLPGNIVSALLMDKIGRLRMLAGSSVMSCVSCFFLSFGNSESAMIALLCLFGG 660

Qy    661 VSIASWNALDVLTVELYPSDKRTTAFGFLNALCKLAAVLGISIFTSFVGITKAAPILFAS 720
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    661 VSIASWNALDVLTVELYPSDKRTTAFGFLNALCKLAAVLGISIFTSFVGITKAAPILFAS 720

Qy    721 AALALGSSLALKLPETRGQVLQ 742
          ||||||||||||||||||||||
Db    721 AALALGSSLALKLPETRGQVLQ 742
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Therefore, Claims 93, 97, 99, and 102 are anticipated by WO2003016475A2.

Claims 93, 97, 99, and 102 are also rejected under 35 U.S.C. 102(a) as being anticipated by WO2003016475A2 published Feb 27, 2003, effective filing date Aug 14, 2001.

WO2003016475 teaches as set forth above. Therefore, Claims 93, 97, 99, and 102 are anticipated by WO2003016475.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 93-102 and 139-156 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO2003016475A2 (published Feb 27, 2003, effective filing date Aug 14, 2001) in view of Margineanu et al. (Antiepileptic Drugs, 5th edition. Levy RH et al. 2002; Lippincott Williams & Wilkins, Philadelphia, PA. P.419-427, as cited in IDS submitted 09/23/04) and Berkower (Curr. Opi. Biotech. 1996.7:622-628).

WO2003016475 teaches as set forth above but fails to teach the screening method is to evaluate the test compound of an analog/derivative of levetiracetam, or a compound competing with the binding of levetiracetam/its derivatives to the binding of levetiracetam to the levetircetam binding site of SV2A. In addition, WO2003016475A2 fails to teach the test compounds for treating neurological disorders have the activity of competing with the levetiracetam binding site of SV2A. WO2003016475A2 also fails to teach that the

test compounds in the screening method is an antibody or humanized antibody that binds to the levetiracetam binding site of SV2A protein.

Margineanu et al teach that levetiracetam (LEV) is an anti-epilepsy drug approved by FDA. LEV can reduce the epilepsy induced by $GABA_A$ receptor antagonists (inhibitors for inhibitory neurotransmission) or NMDA (neurotransmitters for excitatory neurotransmission) (see p. 422, second paragraph). In addition, the drugs inhibiting GABA-related convulsants and T-type Ca^{++} channel can inhibit the binding of LEV to brain membrane (see p. 423, second column, first paragraph). Margineanu et al. further teach that LEV has effects on neurotransmitter receptors and neuron-ion channels and affects high-voltage Ca^{++} currents, GABA-gated currents and AMPA-gated currents, which are the measurements for synaptic transmissions regulated by vesicle exocytosis, a process involved in SNARE complex formation and synaptic vesicles ducking on the plasma membrane (see p. 425, table 40.3 and p. 426, first column second paragraph).

Berkower teaches that monoclonal antibodies are potent tools for diagnosis and disease treatment because they can have effects on immunosuppression, immunotherapy or blocking the interaction between receptor and ligands (seep. 622, introduction). In addition, antibody fragments have better clearance rate and humanized antibodies can avoid the development and the adverse effects of human anti-mouse antibodies for patients (see P. 626, Hybrid immunoglobulins).

It would have been obvious for one of ordinary skill in the art at the time of the instant invention was made to combine the teachings of WO2003016475A2, Margineanu et al. and Berkower to screen a compound or antibody that can compete with the levetiracetam binding site of SV2A for the potential treatment of neurological diseases associated with synaptic function. The person of ordinary skill in the art would have been motivated to make those modifications because it has been shown that levetiracetam affects the synaptic activity regulated by excitatory (AMPA), inhibitory (GABA) synaptic transmission and Ca channels. Since SV2A has been shown to be involved in SNARE complex formation and exocytosis, and synaptic transmission is highly regulated by SNARE complex and vesicle fusion/exocytosis, one of ordinary skill in the art would have expected success in measuring the synaptic activity to screen a compound that is able to regulate/compete the binding of levetiracetam to SV2A. In addition, since the humanized antibodies or antibody fragments have better effects on immunotherapy, it would be obvious for one of ordinary skill in the art to be motivated to screen humanized antibodies that compete with the levetiracetam-binding site of SV2A for treating epilepsy as taught by WO2003016475A2, Margineanu et al. and Berkower.

Claims 93, 126-137 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO2003016475A2 (published Feb 27, 2003, effective filing date Aug 14, 2001) in

view of Xu et al. (Nat. Cell Biol. 2001, 3:691-698, as cited in IDS submitted 09/23/04) and Son et al. (J. Biol. Chem. 2000, 275: 451-460 as cited in IDS submitted 09/23/04).

WO2003016475A2 teaches as set forth above but fails to teach evaluating the activity of SV2A protein by measuring at least one cation/a substrate across a membrane, measuring SNARE complex/Ca^{++} channel formation or synaptic vesicle fusion/recycling.

Xu et al. teach that the role of SV2A in exocytosis using cells derived from SV2A Knock out mice. Xu et al. showed that SV2A is a molecule involved in exocytosis and modulate the formation of SNARE complex for vesicle fusion by measuring the membrane capacitance and Ca^{++} concentration (see p. 692, figures 2 and 5). SV2A modulates synaptic vesicle fusion and its interaction with synaptic protein, synaptotagmin, is Ca^{++}-dependent (see p. 696, discussion), which also affects the Ca^{++} channel activity.

Son et al. teach that SV2A forms a complex with laminin-1 in synaptosome through the direct binding to laminin-1 (see p. 451, abstract).

It would have been obvious for one of ordinary skill in the art at the time of the instant invention was made to combine the teachings of WO2003016475A2, Xu et al. and Son et al. to screening a compound or antibody that can compete with the levetiracetam binding site of SV2A by measuring vesicle exocytosis, which is involved in cation influx/exflux, SNARE complex formation and Ca^{++} channel activity. The person of ordinary skill in the art would have been motivated to measure the molecules/activities involved in exocytosis because

SV2A has been shown to be involved in SNARE complex formation for vesicle fusion and the interaction with SNARE complex is through the interaction with synaptotagamin and Ca^{++}. One of ordinary skill in the art would have expected success in evaluating the binding of test compound to the levetiracetam-binding site of SV2A by measuring the parameters/molecules involved in exocytosis.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30

AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
February 27, 2006

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